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EXAMINER	
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ART UNIT	PAPER NUMBER
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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ~~—~~ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449
4. ☐ Notice of Informal Patent Application, Form PTO-152
5. ☐ Information on How to Effect Drawing Changes, PTO-1474
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-31 are pending in the application.
   Of the above, claims 24-26 are withdrawn from consideration.
2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-23, 27-31 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings which are acceptable for examination purposes until such time as allowable subject matter is indicated.
8. ☐ Allowable subject matter having been indicated, formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. These drawings are ☐ acceptable; ☐ not acceptable (see explanation).
10. ☐ The ☐ proposed drawing correction and/or the ☐ proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved. ☐ disapproved (see explanation). However, the Patent and Trademark Office no longer makes drawing changes. It is now applicant's responsibility to ensure that the drawings are corrected. Corrections MUST be effected in accordance with the instructions set forth on the attached letter "INFORMATION ON HOW TO EFFECT DRAWING CHANGES", PTO-1474.
12. ☐ Acknowledgment is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-23 and 27-31, drawn to recombinant pox virus comprising tumor associated antigens, plasmids comprising DNA encoding the antigens, and methods using the recombinant pox viruses, classified in Class 435, subclasses 68, 172.3,, and 235.

II. Claims 24-26, drawn to methods of producing antibodies and methods using the antibodies, classified in Class 514, subclass 2.

The inventions are distinct, each from the other because of the following reasons:

Inventions I and II are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP 806.05(h)). In the instant case the product as claimed may be used in a materially different process, such as in a process for producing the antigen encoded by the recombinant vaccinia virus.

During a telephone conversation with Mr. Diconti on 3/89 a provisional election was made with traverse to prosecute the invention of group I, claims 1-23 and 27-31. Affirmation of this election must be made by applicant in responding to this office action. Claims 24-26 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and divergent subject matter, and because the searches for the individual Groups are not coextensive, restriction for examination purposes as indicated is proper.

35 U.S.C. 101 reads as follows:
"Whoever invents or discovers any new and useful process. machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title".

Claims 15 and 22 are rejected under 35 U.S.C. 101 because there is no evidence that the claimed invention is operable. Claims 15 and 22, thus, lack patentable utility.

Claims 15 and 22 are directed to methods for immunizing an individual against a tumor-specific antigen who is afflicted with

a tumor that expresses the antigen. There is nothing in the specification from which it may be inferred that inoculating such an individual with a recombinant vaccinia virus comprising said antigen will immunize the individual against the tumor-associated antigen present on the surface of the tumor. An individual afflicted with such a tumor would have already, if possible, mounted an immunological response against the antigen. Immunization with DNA encoding the antigen may hinder this response by binding to existing antibodies.

The following is a quotation of the first paragraph of 35 U.S.C. 112: The specification shall contain a written description of the invention, and the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide an enabling disclosure and an adequate written description of the invention because it does not appear that applicant has provided the complete chemical structure or the complete nucleotide sequence of the biological material, such as ABT9-4, pEVAC-neu, or vaccinia virus

comprising any other tumor-associated antigen, that is essential for practicing the claimed invention.

A deposit of biological material is generally required when all of the starting material are not available to the public and/or when applicant has not presented the complete nucleotide sequence of the DNA or the complete chemical structure of the biological material that is essential for practicing the claimed invention. A deposit must satisfy the availability and maintenance requirements of MPEP 608.01(p)(C). It is sufficient if a statement is made by applicant, applicant's attorney of record, or assignee's representative that a deposit has been accepted under the Budapest Treaty under conditions that all restrictions upon the availability to the public of the deposit will be irrevocably removed upon the granting of the patent. This means that a viable deposit has been made (Rule 10) in an acceptable depository (INA) for a period of five years after the most recent request and at least 30 years from the date of deposit (Rule 9) under conditions that access to the deposit will be available during the pendency of the patent application to one determined by the Commissioner to be entitled thereto under 37 CFR 1.14 and 35 USC 122 (Rule 11.1), and that all restrictions will be removed once the patent is granted. Assurance of permanent availability of the deposited material through the depository is reasonably assured through the deposit of a viable culture under the Budapest Treaty. In addition, if a deposit has

not been made prior to the effective filing date of the instant application, it is necessary to establish the chain of custody of the material from said date until the material is deposited.

The specification further fails to provide an enabling disclosure and an adequate written description of the invention because it is unclear what applicant contemplates "tumor-associated antigen" to encompass. Are all growth factor receptors tumor associated antigens? Are all tumor associated proteins antigenic? If not how is one of skill in the art to recognize which are antigenic? It is also unclear what applicant means by an oncogene that is "devoid of oncogenic activity" (see, e.g. claim 11).

The specification further fails to provide an enabling disclosure and an adequate written description of the invention because the specification does not teach the immunization of any individual against a tumor-associated antigen nor does it teach how to identify what antigen is borne by the tumor with which the individual is afflicted. It is also unclear what it means to be immunized against an antigen that is associated with a tumor. In addition, the specification does not teach recombinant vaccinia virus comprising the ros gene, the trk gene, the kit gene, the c-erbB gene, any oncogenes (other than neu) or proto-oncogenes, or any growth factor receptors, or growth factor receptor-like surface molecules. It is also unclear what a growth factor receptor-like surface molecule is and whether or

growth factor receptors and growth factor receptor-like molecules are tumor antigen. It is also unclear what applicant means by a plasmid vector (see e.g., claim 28). How does it differ from a plasmid or a vector? The specification does not teach vaccinia virus comprising more than one tumor-associated antigen gene nor vectors for the insertion of more than one heterologous gene. Finally, the specification does not teach the production of any cell-encoded tumor-associated antigen (claim 23).

Claims 1-23 and 27-31 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1-13,15-23,27-30 are rejected under 35 U.S.C. 112, first paragraph, as the disclosure is enabling only for claims limited to pEVAC-neu, ABT 9-4, and to methods for immunizing mice against the tumorigenicity of neu transformed NIH 3T3 cells that are administered subsequent to immunization.. See MPEP 706.03(n) and 706.03(z).

The specification only discloses the construction of recombinant vaccinia virus comprising the neu gene and the use thereof to immunize mice; whereas, the claims read on recombinant pox viruses comprising DNA encoding any tumor-associated antigen and the use thereof to immunize individuals against any tumor-associated antigen.

In Ex parte Forman, 230 USPQ 546 (Bd. App. 1986), the Board considered the issued of enablement in molecular biology.

The Board summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and, (h) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, results of experiments in molecular biology are unpredictable.

In instant case the specification does not teach any other pox virus vectors or how such may be used as cloning vectors because the specification does not teach means to identify promoters and non-essential regions of any pox virus. In addition, the specification does not teach means to attenuate the virulence of any pox vector nor that individuals that are vaccinated against vaccinia virus are resistant to infection with any pox virus. Vaccinia virus is chosen as a vector because virtually all adults are resistant to infection thereby. The specification also does not teach means to identify and clone any tumor-associated antigen nor does it teach DNA encoding any antigens, other than neu. The cloning and expression of heterologous genes is an inherently unpredictable process. It is first necessary to construct a probe that will hybridize to the gene of interest, if the amino acid sequence is known, or devise

an assay or other means of identifying and selecting the gene. The gene must then be subcloned into a vector and not deleted by the recombinational events necessary to insert it into a viral vector, such as a pox vector. In instant case applicant has only taught DNA encoding one gene, but the claims read on DNA encoding any tumor-associated antigen. For these reasons it would require undue experimentation for one having skill in the art to identify, isolate and clone DNA encoding any tumor-associated antigen into any pox virus vector and to immunize an individual against any tumor-associated antigen. The claims are, thus, broader than the enabling disclosure. See, e.g., Ex parte Forman, supra.

Claims 1-23 and 27-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite in the recitation of "cell-encoded, tumor-associated antigen" because it is unclear what is meant by "cell-encoded". It the antigen encoded by the host's cells or by the tumor's cells? Claims 2 and 16 are indefinite in the recitation of "of the species vaccinia". Does this mean that it is a vaccinia virus vector? Claims 3 and 18 are indefinite in the recitation of "human oncogene and is rendered inactive with respect to its oncogenic activity" because it is unclear and unascertainable what it means for an oncogene to be rendered

inactive and what is meant by oncogenic activity. Claims 5,10,19, and 30 are indefinite in the recitation of "portion thereof" or "portions thereof" because it is unclear and unascertainable how many nucleotides a portion consists. Is one nucleotide a portion? Claims 6,7,12, and 20 are indefinite in the recitation of "growth factor receptor-like cell surface molecule" because it is unclear and unascertainable what a receptor-like cell surface molecule is. Claims 27-30 are indefinite and incomplete in failing to specify the physical relationships among the claimed elements. Claim 30 is also indefinite in the recitation of "d. DNA sequences . . . and 3' ends" because it is unclear what this means. What sequences flank the promoter? What 5' and 3' ends? How can an inserted DNA sequence be at both the 5' and 3' ends of the region in which it is inserted? Claim 28 is indefinite in failing to provide proper antecedent basis for "plasmid vector of claim 27" because claim 27 is directed to a vector for recombination with a pox virus".

Claims 5,7,9,10,13,19,21, and 30 are rejected under 35 U.S.C. 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim. These claims do not further limit the claims upon which they respectively depend because they are directed to tumor-associated antigens that are not cell-encoded and the claims upon which they depend are limited to cell-encoded tumor-associated antigens.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless-

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

A person shall be entitled to a patent unless

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office Action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f)

> and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

Claims 1-24 and 27-31 are rejected under 35 U.S.C. 102(a) as anticipated by or, in the alternative, under 35 U.S.C. 103 as obvious over Lathe.

Lathe discloses recombinant vaccinia viruses comprising T-associated antigens and the use thereof to immunize susceptible animals against the tumors associated with the antigens. In the absence of unexpected results the particular tumor-associated antigen chosen for subcloning into vaccinia virus vectors is a matter of arbitrary experimental design choice and is, thus, obviated by Lathe.

Claims 1-24 and 27-31 are rejected under 35 U.S.C. 103 as being unpatentable over Kornbluth or Mansour in view of Davis and Paoletti.

Paoletti teaches recombinant vaccinia viruses and methods for their construction by recombination with a plasmid that comprises vaccinia virus DNA sequence derived from a non-essential region flanking the heterologous gene that is to be inserted into the vaccinia virus. Paoletti also teaches that these vectors are designed to express heterologous antigens and to be used as vaccines. Kornbluth teaches the construction of a retroviral vector that comprises the polyoma middle T antigen in place of the v-src gene nd the use thereof to induce tumors in 1

week old chickens. Davis teaches that adult mice immunized with polyomavirus (page 541) elicit either no tumors or tumors that regress, leaving a high level of specific immunity to the tumor specific antigen and 2) that virus infected cells produce three T (tumor) antigens: large T, small T and middle T. Davis also teaches that adult mice immunized with polyomavirus (page 541) or tumor cell extracts (page 1259) elicit either no tumors or tumors that regress, leaving a high level of specific immunity to the tumor specific antigen, that tumor-associated antigens distinguish tumor cells from normal cells and that these antigens induce immune responses in tumor bearing hosts (page 540), and that virus infected cells produce three T (tumor) antigens: large T, small T and middle T. Thus, Davis teaches not only motivation to immunize animals with tumor specific antigens in order to elicit tumoral immunity, but also teaches the tumor specific T antigens which can be used for such immunizations.

In view of the teaching of Davis that viruses comprising DNA encoding T antigens can be used to immunize against tumor development it would have been obvious to one of ordinary skill in the art to have used known viral vectors that are designed for use as vaccines, such as the vaccinia virus vectors constructed as taught by Paoletti, comprising DNA encoding a tumor-associated antigen, such as the T-antigens, in order to immunize animals. Baring unexpected results, the production of recombinant vaccinia virus vectors comprising known DNA encoding

antigens and the use thereof for immunization are well within the skill level of the art.

Any inquiry concerning this communication should be directed to Dr. S. Seidman whose telephone number is 703 557-5137.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is 703 557-0664.

Seidman/seidman 3/25/89

STEPHANIE L. SEIDMAN
EXAMINER
ART UNIT 185